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Effects of a 3-week preoperative home rehabilitation programme in COPD patients eligible for lung cancer surgery: A multicentre randomized controlled trial

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Secondary Subject Heading:	Surgery
Keywords:	exercise, lung resection, physical therapy, postoperative complication, rehabilitation

Dear **Dr T Groves**,

Please find attached an original manuscript related to a research protocol we wish to submit to *BMJ Open* journal.
This protocol deals with a preoperative exercise training programme for chronic obstructive pulmonary disease patients eligible for lung cancer resection. This work is the collaboration of physical therapists, physical MD, surgeons and physiologists. We plan to organize a partially supervised training programme at home in order to improve the adherence without delaying the surgical treatment. This is a hot topic in this setting, as emphasized in recent systematic reviews. We think that this home-based strategy will be successful in decreasing postoperative morbidity and hospital length of stay and could be spread for patients living far from a pulmonary rehabilitation centre.
The english language has been verified by a native english translator.
We conduct this trial in accordance with the Consort recommendations for non-pharmacological trials. We chose to use the Consort checklist for reporting trials of non pharmacologic treatments which is the most adapted for describe an exercise intervention *(Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P, CONSORT Group. Methods and processes of the CONSORT Group: example of an extension for trials assessing nonpharmacologic treatments. Ann Intern Med 2008; 148(4): W60-66.)*.

On behalf of my co-authors, I hereby certify that this manuscript has never been submitted to another journal or been duplicated.

Sincerely yours

H Laurent
PhT

Title: **Effects of a 3-week preoperative home rehabilitation programme in COPD patients eligible for lung cancer surgery: A multicentre randomized controlled trial**

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Effects of a 3-week preoperative home rehabilitation programme in COPD patients eligible for lung cancer surgery: A multicentre randomized controlled trial

ABSTRACT (269 words/300 max)

Introduction: Lung cancer is the 4th most frequent cancer but the 1st cause of cancer-related death worldwide. Surgery is the standard curative treatment but is only possible in patients with local disease and preserved exercise capacity. Improving exercise fitness before surgery was shown to reduce postoperative complications. However, preoperative rehabilitation remains difficult to implement in this setting due to a short period between diagnosis and surgery. Our aim will be to demonstrate that a preoperative home rehabilitation programme reduces hospital length of stay and complication rate in patients eligible for lung cancer resection.

Methods: We designed a multicentre randomized controlled trial. We will recruit 90 patients with Chronic Obstructive Pulmonary Disease diagnosed for lung cancer from four university hospitals. A rehabilitation group (R group) will receive a standardized preoperative home exercise programme for 3 weeks, associating both high-intensity training and conventional physical therapy. R group will perform 15 training sessions on a cycloergometer with heart rate monitoring. A once a week training session will be supervised by a physiotherapist. R group will be compared to a control group receiving preoperative conventional physical therapy only. The primary outcome will be the hospital discharge ability assessed with a 10-

item list. The secondary outcomes will be postoperative course, pre/post-intervention pulmonary function and exercise capacity, and pre/post-operative quality of life.

Conclusion: We hypothesize that the training programme will increase the aerobic capacity which should influence postoperative course. The result of this original trial should confirm safety and feasibility of such short home-based interventions. This will change physiotherapists' practice before lung cancer surgery enabling this intervention to be spread without delaying the surgical treatment.

KEYWORDS: (5/5 max)

exercise, lung resection, physical therapy, postoperative complications, rehabilitation

Ethics and dissemination: This protocol has been approved by the French health authorities (Agence Nationale de la Sécurité du Médicament et des produits de santé # 2016-A00622-49) and by the Committee for Ethics (Comité de Protection des Personnes Sud Est VI France #AU1267). Adverse events which would occur during the protocol (training programme and up to 1 month after hospital discharge) will be reported to the principal investigator and the safety committee. The results will be published in an international peer review journal.

Registration: Clinical Trials # NCT 03020251

STRENGHTS AND LIMITATIONS OF THIS STUDY (3/5 max)

- A multicentre randomized controlled trial
- Large number of participants (n=90 patients)
- This study includes patients presenting lung cancer (or high suspicion for malignant tumour) eligible for resection surgery (lobectomy or pneumonectomy)

1. INTRODUCTION

Lung cancer (LC) is the fourth most frequent cancer in the world, but the first cause of cancer-related death worldwide [1,2]. Among treatments surgery is conducted in a curative intent generally in patients with early TNM disease stages (stages I and II) and good functional status [3]. But, only 25% of patients are considered suitable for surgery [4].

Before surgery all patients have an evaluation of respiratory and cardiovascular functions to assess their operative risk. This is estimated on an algorithm with calculation of predicted values of postoperative pulmonary function based on importance of lung tissue resection [4]. Despite this operative risk assessment, postoperative respiratory complications and overall complications incidence are respectively 15% and 30% after lung resection for cancer [5]. Patients with complicated postoperative course have a longer hospital length of stay, a more frequent stay in intensive care unit (ICU) and a higher mortality rate.

Furthermore, oxygen uptake is reported to be the strongest independent predictor of surgical complications and survival rate in non-small cell lung cancer (NSCLC) [6]. Field tests are equally major determinants of morbidity and mortality after lung resection surgery [6]. Surgery itself initiates a 13% to 28% decrease in oxygen uptake [7], lasting up to 24 months after surgery [8]. The existence of chronic obstructive pulmonary disease (COPD) or cardiovascular comorbidities may generate a further decrease in oxygen uptake [7]. Chemotherapy and/or radiotherapy are associated with additional impairment of exercise capacity [8]. In consequence, a considerable number of patients require preoperative optimization of respiratory and exercise capacity.

Beneficial effects of preoperative rehabilitation are objectified on physiological parameters and surgical outcomes in thoracic surgery (lung transplantation and lung reduction surgery for

emphysema) [4]. Nevertheless, for NSCLC resection the level of evidence is deemed insufficient. Two recent systematic reviews reported that preoperative exercise may have beneficial effects on various physical variables and postoperative complication rate in patients with lung cancer scheduled for surgery [9,10]. The authors emphasize the following points: future research must focus on patient tailored exercise programmes and investigate influence of coexisting comorbidities on outcomes. Definitions of preoperative exercise therapy and exercise modalities including timing and training volume should be detailed and compared. Study must investigate preoperative home rehabilitation in order to integrate patients better in their therapeutic project, to make readaptation programmes more accessible and to reduce costs of such programmes by avoiding hospitalization in readaptation centres. A last review concluded that preoperative rehabilitation for lung resection surgery improves exercise capacity and limits loss of postoperative lung function [11]. On the other hand, benefit for postoperative complications and hospital length of stay remains uncertain, justifying further controlled studies.

In this way, a randomized controlled trial (RCT) [12] implemented a preoperative outpatient intensive rehabilitation programmes in patients with COPD and NSCLC. This was based on high intensity training of both upper and lower limb muscles. Physical performance improved significantly in the rehabilitated group, and its increase persisted even after surgery. So, it seems particularly important to take advantage of the 4-5 weeks before surgery to optimize physical condition and to improve postoperative course of patients resected for lung cancer. It is even more crucial as preoperative rehabilitation may increase the number of patients eligible for surgery. However, rehabilitation programmes are not yet substantially developed. Some consider that it delays surgery, engendering fear for tumour progression which could require heavier action or contraindicate resection. In practice, organizing of such programmes is difficult because local structures able to manage the training programme quickly are

lacking. A study showed the functional benefit of a 4-week training programme performed at home and the feasibility of rehabilitation in this setting before lung cancer resection [13].

Through this prospective, multicentre, randomized, controlled and open-label trial our objective is to reinforce the adherence and the benefits of preoperative rehabilitation in this setting. So we plan a home-based supervised exercise training programme added to the usual care (physical therapy), in order to decrease hospital length of stay and complication rate in COPD patients eligible for lung cancer resection.

2. METHODS

2.1. Setting

This prospective, multicentre, randomized, controlled and open-label trial will be conducted in 4 French University Hospitals.

2.2 Participants

2.2.1. Inclusion criteria

We will include patients presenting the following conditions:

- Lung cancer (or high suspicion for malignant tumour) eligible for resection surgery (lobectomy or pneumonectomy)
- >18 years old
- COPD stages from 2 to 4 on Gold classification (FEV1/FVC<70% of the theoretical value, FEV1<80% of theoretical value)
- Exertional dyspnea stage mMRC≥1
- Receiving written information and giving their signed consent
- Affiliated to the French social health insurance.

2.2.2. Non inclusion criteria

We will not include patients presenting the following conditions:

- COPD stage 1 on Gold classification (FEV1≥80% of the theoretical value)
- Contraindication to surgery based on the initial cardiopulmonary exercise test (CPET)
- Cardiac or vascular contraindication to the rehabilitation programme

- Living alone at home
- Under ventilatory assistance at home [oxygen therapy or non-invasive ventilation (NIV)]
- Exercise hypoventilation ($PaCO_2$>45 mmHg)
- Cognitive impairment
- Legally incapacitated individual
- Pregnancy.

Specific non inclusion criteria for achieving muscle biopsies (in optional ancillary study) will be allergy to xylocaine, coagulation results judged incompatible with the realization of the biopsy.

2.3. Details of the intervention and control

2.3.1. Rehabilitation group

The Rehabilitation group (R group) will realize both a standardized preoperative high intensity training programme performed at home and standardized physical therapy sessions according to the usual care. For 3 weeks the patients will carry out 15 sessions of rehabilitation. The cycloergometer will be installed by the service provider who will organize home care in each centre. These training sessions will be supervised by physical therapists accustomed to these programmes. The study will not lead to delay in the treatment and the surgical management.

The rehabilitation programme will consist in an endurance cycloergometer training with heart rate (HR) monitoring.

The first week of training (W1) will consist of a continuous training regime programme. W1 will permit us to assess the patient's ability to complete his training course and to teach him

how to perform it well. The session will include a 5-minute warm-up, cycloergometer workload fixed to the ventilatory threshold determined during the CPET or at 60% of maximum workload, if the ventilatory threshold was not detectable. The exercise session will last at least 30 minutes which can be separated by rest periods.

The week 2 and 3 of training (W2 and W3) will consist of a high-intensity training regime programme. The reduced volume of training and shorter session duration required with high intensity training to obtain physical benefits versus continuous training should be more acceptable for patients still engaged in several preoperative exams and preoperative care [14]. The longer rest period between each high intensity training session will potentialise recuperation time and will favour the adherence rate for our preoperative rehabilitation programme added on conventional physical therapy sessions [14]. The course of high-intensity sessions will be 30 seconds at maximum workload and 60 seconds at the ventilatory threshold level for at least 10 repetitions.

The intensity of the exercise and the number of peaks will be adjusted weekly based on HR to maintain the target progression of ± 5 beats/min.

A physical therapist accustomed to COPD patients' rehabilitation will visit the patient at home and supervise 3 sessions once a week (at beginning of each of the 3 weeks: the 1st, 6th and 11th exercise session) checking the initial intensity and progression of the sessions. The patient will note on a notebook the duration of the session, the intensity of exercise on the cycloergometer, the mean HR and the number of peaks. We will record the number of realized exercise session(s) effected, the number of exercise session(s) not effected and the reason(s) why they were not effected.

Until the surgery the R group will also perform muscle strengthening exercises for upper limbs using elastic bands and will receive a prescription for usual care (standardized physical therapy).

2.3.2. Control group

The Control group (C group) will carry out 15 standardized preoperative physical therapy sessions according to the usual care. They will be standardized in each centre with a prescription. They will consist of bronchial drainage, incentive spirometry, respiratory muscle training, stretching and global training. According to current recommendations, C group will be advised to be physically active.

2.4. Primary and secondary outcome measures and assessment point

Measurements are presented on *figure 1*. The primary outcome will be the hospital discharge ability assessed with a 10-item list. The secondary outcomes will be postoperative course, pre/post-intervention pulmonary function and exercise capacity, and pre/post-operative quality of life. These outcomes are known to be positively influenced by oxygen uptake, a surrogate of patients' fitness and predictor of surgical complications and survival rate in NSCLC [6]. Moreover, they should be improved by the exercise training programme [9,10].

2.4.1. Primary outcome

Hospital discharge ability assessed daily with a 10-item list will reflect clinical assessments. It should be more relevant than hospital length of stay which is impacted by circumstances independent of patient condition (for example: possibility or not of discharge during the weekend, of therapeutic care at home, of transfer to a rehabilitation centre). The period considered for discharge ability will be the delay between the day of surgery (D0) and the day (Dn) when the 10 items will be satisfied (*Annex 1*).

2.4.2. Secondary outcomes

2.4.2.1. Postoperative course

We will consider the number of postoperative complications (pulmonary, cardiovascular, infectious, and general – see *Annex 2* for respective definitions) observed during the stay in surgery or ICU departments, the mortality rate, the hospital length of stay, the chest tube duration, the number of NIV sessions and the ICU length of stay and it(s) reason(s).

2.4.2.2. Pulmonary function test (PFT)

It will consist of the determining static pulmonary volumes and flow rates (flow/volume curve) according to the international recommendations in a body plethysmograph [15]. A measure of the alveolar-capillary diffusion capacity for carbon monoxide (DLCO) will be carried out by the apnea method. Arterial blood gases (PaO_2, $PaCO_2$, and pH) at rest will be measured either by arterial sampling or arterialized capillary sampling at ear lobe [16]. Maximum respiratory pressures (inspiratory and expiratory pressures at mouth, and nasal inspiratory pressure) will be measured in accordance with the American Thoracic Society and European Respiratory Society recommendations [17].

2.4.2.3. Cardiopulmonary exercise test (CPET)

The patient will perform a test of standardized incremental effort (one minute increments) following the American Thoracic Society and American College of Chest Physician guidelines [18]. It will be realized on a cycloergometer until exhaustion, with continuous recording of 12-lead electrocardiogram and breath-by-breath expired gases analysis [18]. The ventilatory threshold will be determined by the Beaver method. The

maximum parameters are those measured at the end of the last exercise level maintained for at least 30 seconds. We will consider oxygen uptake (VO_2) at the aerobic threshold and at the maximum of exercise, workload at the aerobic threshold and at the maximum of exercise, carbon dioxide consumption (VCO_2), ventilation (VE), HR, rating of perceived exertion (RPE), dyspnea Borg scale and blood gases at the end of maximum exercise test.

2.4.2.4. 6-Minutes Walking Test (6MWT)

The 6MWT will be conducted according to the American Thoracic Society and European Respiratory Society recommendations in an enclosed corridor over a flat, 30 metre course between two cones [19]. Patients will be instructed to cover the longest distance possible in 6 minutes with or without rest. During the test only standardized encouragement will be given to the patient. Pulsed oxygen saturation (SpO_2) and HR will be measured continuously during the test and recorded each minute with a digital oxymeter. The absolute and relative distance (6MWD), SpO_2, HR, rating of modified dyspnea Borg scale, walking duration if cessation test occurs before 6 minutes and reason(s) for this cessation will be recorded.

2.4.2.5. Bioimpedancemetry

Body composition will be assessed performing a multi-frequency bioelectrical impedance analysis in standardized conditions [20–22]. The patient will be placed in supine position on the floor during measurement. We will determine fat free mass, dry fat free mass and fat mass.

2.4.2.6. Maximum voluntary quadriceps isometric strength

The patient will be sat on a recumbent chair with a light kyphosis and arms crossed over the chest [22,23]. The dominant lower limb will be tested with knee placed at 90° of flexion. The order provided by a trained examiner will be standardized to obtain the maximal contraction. The sustained time of contraction will be 5 seconds each and the rest time will be 60 seconds each. The first two attempts will be considered to be for learning. A minimum of four and a maximum of ten attempts will be conducted to ensure three values varying less than 10%. The maximum value obtained will be considered for analysis.

2.4.2.7. Muscles biopsies

For the optional ancillary study, quadricipital and intercostal biopsies will be sampled with the Bergström needle, at inclusion (vastus lateralis) and during the surgical time (both muscles). An average of 100 mg of muscle will be obtained to achieve the usual biological, histological, histochemical analyzes and the oxygraphic permeabilized fibres [24,25] and fluorometric [26] (oxygraph OROBOROS) analysis. This analyses on permeabilized fibres will allow both a dynamic approach to the muscle adaptations and the measure of early markers of response to the training [27].

2.4.2.8. Quality of life (QOL)

We will record the QOL with two validated questionnaires for lung cancer patients. Cancer-related QOL will be assessed using the self-reported European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) including the lung cancer-specific questionnaire QLQ-LC13 [28].

2.4.2.9. Feasibility and safety

To evaluate the feasibility of this protocol we will consider the recruitment rate, the completion rate, and the adherence rate [13]. Recruitment rate will be defined as the ratio of patients who accept to participate in the study to those who are eligible. Completion rate will be defined as the ratio of patients who complete the whole intervention to those who realize the first intervention session. Adherence rate will be defined as the ratio of the number of completed intervention sessions to the number of expected sessions. Adherence will be considered as acceptable when 11 intervention sessions will be realized out of the 15 expected sessions. Adverse events will be systematically tracked during the complete study period and follow up.

2.5. Recruitment procedures

The French classification of the study is interventional but does not involve a health product. It will be conducted in accordance with the Consort recommendations for non-pharmacological trials [29,30]. The study protocol was approved by the French regulatory authority for research (Agence Nationale de Sécurité du Médicament et des produits de santé, Registration number: 2016-A00622-49) and the Committee for Ethics (Comité de Protection des Personnes Sud Est VI France, Human research ethics approval number: AU1267). All patients will receive an information form and be required to provide their written consent before entering this study protocol and performing any specific procedure. After the first surgical visit and the verification of the eligibility criteria, patients eligible for this protocol will be offered to participate. Patients agreeing to participate and having signed informed consent will be directed to the physiology lab for the first protocol visit (pre-intervention) before being assigned to one of the two study groups.

2.6. Randomization and allocation procedures

Randomization will be realized after recruitment procedure with a 1: 1 ratio, stratified by centre, centralized and performed by block of 5. Randomization and allocation sequence will be electronically generated by the research manager.

2.7. Masking/blinding

In such an experiment blinding is not feasible for patient and physical therapist or assessor. However, the C group receiving usual care will make it possible to demonstrate the beneficial effect obtained in the R group.

2.8. Anticipated date of trial commencement and completion

The study will start in April 2017 and will be completed in April 2019.

2.9. Statistical analysis including sample size calculation

Previous studies found a 4-days reduction of length of stay in patients completing an exercise training programme compared to usual care [31,32]. We choose a more conservative effect of the intervention. Our hypothesis is based on a one-sided decrease of 2 days duration of hospital length of stay and considering a standard deviation of 3 days. With a 90% power and a one-sided 5% type one error, 39 patients per group are required. Given a risk of drop out or incomplete programme adhesion (less than 11 sessions effectively made), we plan to increase the sample by 15% i.e. 45 patients per group (total number = 90 patients).

The analysis will be performed intent-to-treat. Patients' characteristics per allocation group will be described using means, standard deviation, and range for quantitative outcomes, or median and interquartile intervals in case of non-Gaussian distribution. For categorical parameters, counts and frequencies will be reported. The balance of main clinical parameters between allocation groups will be studied to verify randomization efficacy. Equilibrium of missing data will be checked in order to assess if any attrition bias could lower the quality of conclusions. The primary outcome being hospital discharge ability, a Student's t-test (unpaired) or Kruskal-Wallis H-test and Mood test (in case of abnormal distributions and/or heteroscedasticity) will be used to test the inter-group difference. Other quantitative outcomes (PFT, oxygen uptake, 6MWD, maximal respiratory pressures, maximum quadriceps voluntary strength, body composition and muscle enzyme activities) will be analyzed using the same tests. The inter-group difference for postoperative complication and mortality rates will be tested using Chi^2 test or Fisher exact test. Multivariate analysis of factors influencing either length of stay or morbidity/mortality will be performed using respectively ANOVA (mixed model) and logistic regression. The standard two-sided $p < 0.05$ will be used as significance cut-off. Clinsight software will be used for randomization and data-management [Ennov Clinical v7.5, Ennov Group, Paris, France] and SEM software for statistical calculation [33].

3. DISCUSSION

Beneficial effect of a short preoperative rehabilitation programme on length of stay after lung cancer resection in COPD patients is still remaining to be robustly demonstrated. Improvement in physical fitness and decrease in complication rate are well shown after an exercise programme in this setting [9,10]. Improving the prepoperative physical fitness in this specific population should limit the loss of postoperative respiratory function and exercise ability [12]. Other studies are needed to demonstrate that the patients who undergo preoperative rehabilitation have a better QOL and a longer survival after lung surgery [12]. The safety and the feasibility of such standardized preoperative programme conducted at home for patients resected for lung cancer should be confirmed despite they have been demonstrated [13]. To our knowledge, it the first time that a multicenter randomized trial will implemented a such preoperative high intensity exercise programme at home in daily lung cancer patient environment, for a such short training period not compromising surgical procedure. The results of this original trial should confirm the safety and feasibility of such short home-based interventions. This will change physiotherapists' practice before lung cancer surgery enabling this intervention to be spread without delaying the surgical treatment.

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CONTRIBUTORSHIP STATEMENT

HL, RR, FK, FC, MF designed the study and wrote the protocol.

GG, ET, EC, SA read and corrected the drafts.

COMPETING INTEREST

None to declare

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DATA SHARING STATEMENT

Not applicable

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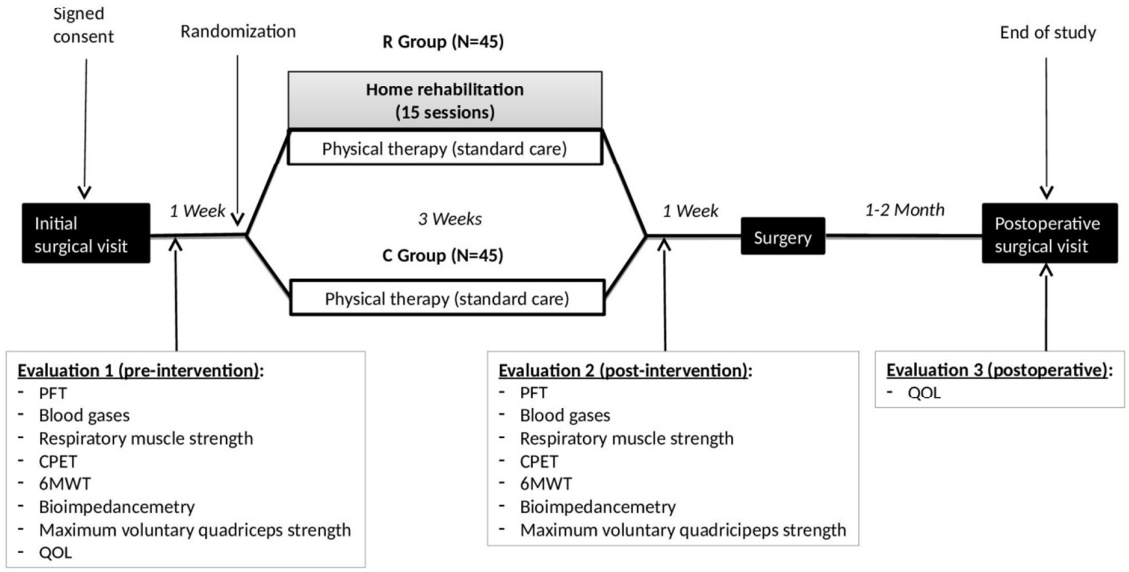
FIGURE 1: Design and outcomes



Abbreviations:

C Group: Control Group

CPET: Cardiopulmonary Exercise Test

PFT: Pulmonary Function Test

QOL: Quality Of Life

R Group: Rehabilitation Group

6MWT: 6-Minutes Walking Test

ANNEX 1: The 10-item list to assess the hospital discharge ability

The criteria considered for hospital discharge ability will be:

- No chest tube for at least 24 hours
- Autonomy for feeding
- Autonomy for up from bed
- Autonomy for toilet
- Autonomy for urinate and defecate
- Patient able to walk (2 lanes 30 meters) without desaturation <90% on room air
- Patient able to go up and down one stair without desaturation <90% on room air (except handicap in which we consider the return to preoperative status)
- Satisfactory healing (parietal, thoracic and bronchopulmonary)
- No infusion
- No oxygen therapy

ANNEX 2: Definitions for postoperative complications

- **Respiratory postoperative complications:**
  - Atelectasis: systematized ventilatory disorder objectified by chest radiography requiring enhanced management such as additional physical therapy sessions, bronchoscopy associated or not with non-invasive ventilation, maintenance or transfer to an intensive care unit
  - Significant bronchial congestion characterized by difficult or spontaneous expectoration of bronchial secretions requiring enhanced management such as additional physical therapy sessions, bronchoscopy with or without non-invasive ventilation, maintenance or transfer to an intensive care unit
  - Bronchospasm: occurrence or aggravation of dyspnea, wheezing at auscultation requiring a specific treatment
  - Respiratory failure requiring management in an intensive care unit for non-invasive ventilation or intubation

- **Cardiovascular postoperative complications:**
  - Pulmonary embolism proven by angio-CTscan
  - Acute coronary syndrome
  - Circulatory failure defined by the need for specific inotropic treatment
  - Rhythm disorder requiring specific treatment

- **Infectious postoperative complications:**
  - Tracheobronchial infection, suspicion of pulmonary infection requiring antibiotic treatment, fever >38.5 °C, dirty sputum, hyperleucytosis >10 000/mm^3, dubious radiological image, absence of pathogenic germs after culture of sputum and/or endobronchial samples
  - Postoperative pneumopathy: pulmonary infection requiring specific antibiotic treatment due to the presence of a pathogenic germs found after culture of sputum and/or endobrochial samples, associated with at least 2 other signs (a fever >38.5 °C, dirty sputum, hyperleucytosis >10 000/mm^3, dubious radiological image)
  - Pneumopathy considered to be nosocomial (occurring after the 5th postoperative day)
  - Pleurisis requiring punction or redrainage for lobectomies

- **Other postoperative complications:**
  - Empyema
  - Bronchopleural fistula
  - Other (for example: urinary tract infection, bleeding)

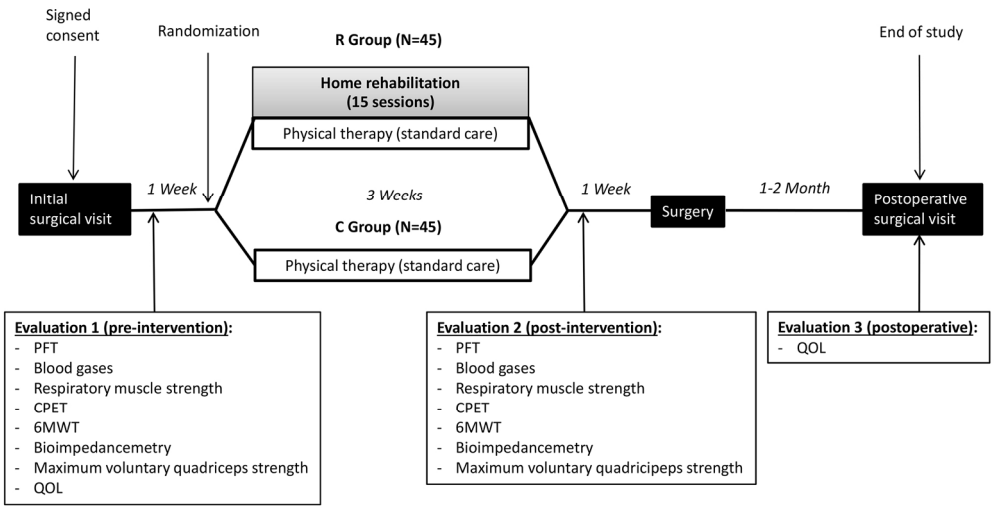


Figure 1: Design and outcomes

173x129mm (300 x 300 DPI)

Checklist of Items for Reporting Trials of Nonpharmacologic Treatments*

Section	Item	Standard CONSORT Description	Extension for Nonpharmacologic Trials	Reported on Page No.
Title and abstract†	1	How participants were allocated to interventions (e.g., "random allocation," "randomized," or "randomly assigned")	In the abstract, description of the experimental treatment, comparator, care providers, centers, and blinding status	1-2
Introduction				
Background	2	Scientific background and explanation of rationale		4-6
Methods				
Participants†	3	Eligibility criteria for participants and the settings and locations where the data were collected	When applicable, eligibility criteria for centers and those performing the interventions	7, 8
Interventions†	4	Precise details of the interventions intended for each group and how and when they were actually administered	Precise details of both the experimental treatment and comparator	8-10
	4A		Description of the different components of the interventions and, when applicable, descriptions of the procedure for tailoring the interventions to individual participants	8-10
	4B		Details of how the interventions were standardized	8-10
	4C		Details of how adherence of care providers with the protocol was assessed or enhanced	Not applicable
Objectives	5	Specific objectives and hypotheses		6
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors)		10-14
Sample size†	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	When applicable, details of whether and how the clustering by care providers or centers was addressed	15-16

Randomization–sequence generation†	8	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification)	When applicable, how care providers were allocated to each trial group	15
Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned		15
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups		15
Blinding (masking)†	11A	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment	Whether or not those administering co-interventions were blinded to group assignment	15
	11B		If blinded, method of blinding and description of the similarity of interventions†	Not applicable
	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses	When applicable, details of whether and how the clustering by care providers or centers was addressed	15-16
Results				
Participant flow†	13	Flow of participants through each stage (a diagram is strongly recommended)---specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome; describe deviations from study as planned, together with reasons	The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center	Not applicable
Implementation of intervention†	New item		Details of the experimental treatment and comparator as they were implemented	Not applicable
Recruitment	14	Dates defining the periods of recruitment and follow-up		Not applicable
Baseline data†	15	Baseline demographic and clinical characteristics of each group	When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group	Not applicable

Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether analysis was by "intention-to-treat"; state the results in absolute numbers when feasible (e.g., 10/20, not 50%)		Not applicable
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (e.g., 95% confidence interval)		Not applicable
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory		Not applicable
Adverse events	19	All important adverse events or side effects in each intervention group		Not applicable
Discussion				
Interpretation†	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes	In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group	Not applicable
Generalizability†	21	Generalizability (external validity) of the trial findings	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial	17
Overall evidence	22	General interpretation of the results in the context of current evidence		17

*Additions or modifications to the CONSORT checklist. CONSORT = Consolidated Standards of Reporting Trials.
†This item was modified in the 2007 revised version of the CONSORT checklist.

BMJ Open

Effect of an intensive 3-week preoperative home rehabilitation programme in COPD patients eligible for lung cancer surgery: A multicentre randomized controlled trial

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Surgery
Keywords:	exercise, lung resection, physical therapy, postoperative complication, rehabilitation

Title: **Effect of an intensive 3-week preoperative home rehabilitation programme in COPD patients eligible for lung cancer surgery: A multicentre randomized controlled trial**

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Effect of an intensive 3-week preoperative home rehabilitation programme in COPD patients eligible for lung cancer surgery: A multicentre randomized controlled trial

ABSTRACT (286 words/300 max)

Introduction: Surgery is the standard curative treatment for lung cancer but is only possible in patients with local tumour and preserved exercise capacity. Improving fitness before surgery can reduce postoperative complications and mortality. However, preoperative rehabilitation remains difficult to implement for several reasons. We aim to confirm the effectiveness of an intensive 3-week home-based preoperative exercise training programme on hospital discharge ability, postoperative complications and physical performance in patients with chronic obstructive pulmonary disease (COPD) who are eligible for lung cancer surgery.

Methods: We designed a multicentre randomized controlled trial. The randomization sequence will be generated and managed electronically by a research manager independent of assessments or interventions. We will recruit 90 patients with COPD and a diagnosis of lung cancer from four university hospitals. The rehabilitation group (R group) will receive a standardized preoperative home exercise programme for 3 weeks, combining both high-intensity training and usual physical therapy. The R group will perform 15 training sessions over 3 weeks on a cycloergometer. A physical therapist experienced in pulmponary rehabilitation will visit the patient at home and supervise one session a week. The R group will be compared to a control group receiving preoperative usual physical therapy only. The primary outcome will be hospital discharge ability assessed with a 10-item list. Secondary outcomes will be postoperative course (complication rate and mortality) as well as pulmonary

function, exercise capacity and quality of life assessed 1 month before and the day before surgery.

Conclusion: The results of this original multicentre randomized trial of home-based rehabilitation should confirm the effectiveness of a short intensive home-based intervention for COPD patients eligible for lung cancer surgery. They could change practice before lung cancer resection thereby enabling preconditioning without delaying surgical treatment.

KEYWORDS (5/5 max): exercise, lung resection, physical therapy, postoperative complications, rehabilitation

ETHICS AND DISSEMINATION: This protocol has been approved by the French health authority (Agence Nationale de la Sécurité du Médicament et des produits de santé, registration no.: 2016-A00622-49) and the Committee for Ethics (Comité de Protection des Personnes Sud-Est VI France, registration no.: AU1267). Adverse events that occur during the protocol (training programme and up to 3 months after hospital discharge) will be reported to the principal investigator and the safety committee. The results will be published in an international peer-reviewed journal.

Registration: Clinical Trials, no.: NCT 03020251

STRENGTHS AND LIMITATIONS OF THIS STUDY (4/5 max)

- A multicentre randomized controlled trial
- Large number of participants (n=90 patients)
- Including COPD patients presenting lung cancer (or high suspicion for malignant tumour) eligible for resection surgery (lobectomy or pneumonectomy with video-assisted thoracic surgery or open thoracotomy)
- No blinding

1. INTRODUCTION

Lung cancer is the fourth most frequent cancer in the world but the first cause of cancer-related death worldwide [1,2]. Among treatments, surgery is conducted with a curative intent generally in patients with early TNM disease stages (stages I, II and IIIA) and preserved exercise capacity [3]. However, only 25% of patients are considered suitable for surgery because of advanced-stage disease or poor functional status [4].

Before surgery, all patients undergo an evaluation of respiratory and cardiovascular functions to assess their operative risk. This risk is estimated by an algorithm with calculation of predicted values of postoperative pulmonary function based on the extent of lung tissue resected [4]. Despite this operative risk assessment, the incidence of postoperative respiratory complications and overall complications are respectively 15% and 30% after lung resection for cancer [5]. Patients with a complicated postoperative course have a longer hospital length of stay, more frequent stay in an intensive care unit (ICU) and higher mortality rate [5].

Furthermore, peak oxygen uptake (VO2peak) is reported to be the strongest independent predictor of surgical complications and survival rates with non-small cell lung cancer (NSCLC) [6]. Performance during field tests are equally major determinants of morbidity and mortality after lung resection [6]. Surgery itself leads to a 13% to 28% decrease in VO2peak [7], lasting up to 24 months after resection [8]. The existence of chronic obstructive pulmonary disease (COPD) or cardiovascular comorbidities may further decrease VO2peak [7]. Chemotherapy and/or radiotherapy are associated with additional impairment of exercise capacity [8].

The beneficial effects of preoperative rehabilitation are objectified by physiological parameters and surgical outcomes in thoracic surgery (lung transplantation and lung volume reduction surgery for emphysema) [4]. Nevertheless, for NSCLC resection, the level of evidence is deemed insufficient [9–11]. A recent Cochrane review emphasized the need for

larger high-quality randomized controlled trials (RCTs) in this area and the disparities between studies [11]. Recent systematic reviews reported that preoperative exercise may have beneficial effects on various physical variables and postoperative complication rates in patients with lung cancer who are scheduled for surgery [9–11]. Interestingly, preoperative rehabilitation for lung resection surgery improves exercise capacity and limits the loss of postoperative lung function [12]. Authors highlight that future research must focus on patient-tailored exercise programmes and investigate the influence of coexisting comorbidities on outcomes. Moreover, preoperative exercise therapy and exercise modalities including timing and training volume should be detailed and compared. Preoperative home rehabilitation should be particularly investigated to make readaptation programmes more accessible and to reduce costs for in- and/or outpatient programmes. Finally, preoperative rehabilitation improves patients' physical fitness and VO2peak and increases the number of patients eligible for surgery [13].

Additionaly, rehabilitation programmes are not yet substantially developed, primarily because of fear of tumour progression by delaying surgery and the difficulty in organizing such programmes or the lack of experienced physical therapists.

Nevertheless, the feasibility, safety and effectiveness of preoperative interventions performed in a home setting for a short period have been demonstrated. An intensive 3-week preoperative high-intensity training programme for outpatients showed significantly improved physical performance, which remained increased after surgery [14]. Moreover, a 4-week training programme performed at home confirmed this benefit on functional outcomes and the feasibility of rehabilitation in this setting before lung cancer resection [15].

In light of the current literature, we implemented a multicentre RCT of an intensive 3-week preoperative home rehabilitation programme for COPD patients eligible for lung

resection. We aim to confirm the effectiveness of a home-based preoperative exercise training programme on hospital discharge ability, postoperative complications and physical performance.

2. METHODS

2.1. Setting

This prospective, multicentre, open-label RCT will be conducted in 4 French university hospitals.

2.2 Participants

2.2.1. Inclusion criteria

We will include patients with the following conditions:

- Lung cancer (or high suspicion for malignant tumour) eligible for resection surgery (lobectomy or pneumonectomy with video-assisted thoracic surgery or open thoracotomy)
- COPD stages from 2 to 4 by the Gold classification (FEV1/FVC<70%, FEV1<80% of predicted value)
- Exertional dyspnea stage mMRC≥1
- Receiving written information and giving signed consent
- Affiliated with the French social health insurance.

2.2.2. Non-inclusion criteria

We will exclude patients with the following conditions:

- COPD stage 1 by the Gold classification (FEV1≥80% of predicted value)
- Contraindication to surgery based on the initial cardiopulmonary exercise test (CPET)
- Cardiac or vascular contraindication to the rehabilitation programme
- Living alone at home (to ensure safety during the training sessions)
- Under ventilator assistance at home [oxygen therapy or non-invasive ventilation (NIV)]

- Exercise hypoventilation ($PaCO_2$>45 mmHg)
- Cognitive impairment
- Legally incapacitated
- Pregnant.

2.3. Details of the intervention and control

2.3.1. Rehabilitation group

The rehabilitation group (R group) will undergo both a standardized preoperative high-intensity training programme performed at home and standardized physical therapy sessions according to usual care. Over 3 weeks, the patients will perform 15 sessions of rehabilitation (5 days/week) including three supervised sessions performed once a week. The cycloergometer will be installed by the service provider who will organize home care in each centre. These training sessions will be supervised by physical therapists familiar with these programmes. The study will not lead to delay in the treatment and the surgical management.

The rehabilitation programme will involve endurance cycloergometer training with heart rate (HR) monitoring.

The first week of training (W1) will consist of a continuous endurance training regime. W1 will allow for assessing the patient's ability to complete the training course and to teach them how to perform it well. The session will include a 5-min warm-up cycloergometer workload fixed to the ventilatory threshold determined during the CPET or at 60% of maximum workload, if the ventilatory threshold was not detectable. The exercise session will last at least 30 min, which can be separated by rest periods.

Weeks 2 and 3 of training (W2 and W3) will consist of a high-intensity interval training regime. The reduced volume of training and shorter session duration required with high-intensity interval training to obtain physical benefits versus continuous training should

be more acceptable for patients still engaged in several preoperative exams and preoperative care [16]. The longer rest period between each high-intensity interval training session will optimize recuperation time and favour adherence [16]. The course of high-intensity sessions will be at least 10 repetitions of 30 sec at maximum workload and 60 sec at the ventilatory threshold level.

The intensity of the exercise and number of repetitions will be adjusted weekly to maintain the targeted HR within 5 beats/min.

A physical therapist experienced in pulmponary rehabilitation will visit the patient at home and supervise one session a week (at the beginning of each of the three weeks: the 1st, 6th and 11th exercise session). The therapist will check the initial intensity and progression of the training sessions. Non-supervised sessions will be performed during the week and not during the weekend to allow for email or phone contact with the physical therapist. The patient will complete a diary to collect the duration and intensity of the cycling exercise, mean HR and number of repetitons. We will record the number of exercise session(s) performed and the reason(s) for not performing exercise.

The rehabilitation programme will also include muscle strengthening exercises for upper arms and standardized usual physical therapy.

Upper-arm exercises will be performed on the same days as after the cycling exercise. Muscles for shoulder (deltoid, pectoral and dorsal muscles), elbow (biceps and triceps muscles), wrist (flexors and extensors muscles) will be trained with elastics or dumbbells. For each muscle groups, 3-5 sets of 8-10 repetitions will be performed starting with the lowest resistance. Depending on the patient perception, the resistance will be increased.

2.3.2. Control group

A control group (C group) will perform 15 standardized preoperative physical therapy sessions according to usual care. The sessions will consist in 30 min performed 5 days/week for 3 weeks. They will be standardized with a written prescription and will include airway clearance techniques, deep breathing exercises emphasizing inspiration, thoracic stretching and upper- and lower-limb stretching. According to current recommendations, the C group will be advised to be physically active.

2.4. Primary and secondary outcome measures and assessment point

Measurements are presented in *figure 1*. The primary outcome will be hospital discharge ability assessed by a 10-item list. The secondary outcomes will be postoperative course (complication rate and mortality), pulmonary function, exercise capacity, and quality of life. Surgical complications and survival rate with NSCLC are predicted by VO2peak, a surrogate of patient fitness [6]. Thus, postoperative morbidity should be improved by the exercise training programme [9,10].

Participants will undergo all assessments in the physiology laboratory on the same day so as to limit transport and fatigue. Baseline assessments will be performed 1 month before surgery (pre-intervention or first evaluation) and will be renewed the day before surgery (post-intervention or second evaluation). To ensure reproductibility of the assessments, the order will be standardized: pulmonary function tests, maximal respiratory pressure measurements, cardiopulmonary exercise test, 6-min walk test (6MWT), bioimpedancemetry, maximum voluntary isometric quadriceps strength measurement and quality of life. The rest period will be respected according to patients' needs.

2.4.1. Primary outcome

We will consider hospital discharge ability assessed by a 10-item list that reflects clinical assessments. Our 10-item list assessing hospital discharge ability was developed by a panel of caregivers including thoracic surgeons, physiologists, a physical medicine physician and physical therapists. We considered this outcome to be more relevant than true hospital length of stay, which is affected by circumstances independent of patient condition (e.g., possibility or not for discharge during the weekend, therapeutic care facilities at home, transfer to a rehabilitation centre). The period considered for discharge ability will be the interval between the day of surgery (D0) and the day (Dn) when the 10 items are satisfied (*Table 1*). It will be recorded daily by caregivers of the surgical staff in charge of the patient.

2.4.2. Secondary outcomes

2.4.2.1. Postoperative course

The postoperative course will be assessed daily by caregivers of the surgical staff in charge of the patient and by information from the patient's file. We will record the number of postoperative complications (pulmonary, cardiovascular, infectious, and general – see *Table 2* for respective definitions [17,18]) observed during the stay in surgery or ICU departments, mortality rate, hospital length of stay, chest tube duration, number of NIV sessions, ICU length of stay and reasons.

2.4.2.2. Pulmonary function test (PFT)

The test will determine static pulmonary volumes and flow rates (flow/volume curve) according to international recommendations by use of a body plethysmograph (Bodybox Jaeger Care fusion, USA) [19]. A measure of the alveolar-capillary diffusion capacity for carbon monoxide (DLCO) will involve the apnea method. All measurements will be expressed as a percentage of reference values [20]. Arterial blood gases (PaO_2, $PaCO_2$, and

pH) at rest will be measured by arterial sampling or arterialized capillary sampling at the ear lobe [21]. Maximum respiratory pressures (inspiratory and expiratory pressures at mouth, and nasal inspiratory pressure) will be measured in accordance with the American Thoracic Society and European Respiratory Society recommendations [22] and compared with predicted values [23].

2.4.2.3. Cardiopulmonary exercise test (CPET)

The patient will perform a standardized incremental test following the American Thoracic Society and American College of Chest Physician guidelines [24]. The test will be performed on a cycloergometer until exhaustion, with continuous recording by 12-lead electrocardiography and breath-by-breath expired gas analysis (CPX MedGraphics, St Louis, USA) [24]. The workload increments will be defined according to predicted maximal power output (Wmax), with a first stage of warm-up corresponding to 30% Wmax and 10 following stages to complete the test in 12 to 15 min. The ventilatory threshold will be determined by the Beaver method. Wmax and VO2peak will be measured at the end of the last exercise level maintained for at least 30 sec. Symptoms will be rated on a 10-point Borg scale. Blood gases will be measured at the end of the test. Reference values for exercise testing values will be from Jones [25].

2.4.2.4. 6-min walk test (6MWT)

The 6MWT will be conducted according to the American Thoracic Society and European Respiratory Society recommendations in 30-m corridor [26]. Patients will be instructed to cover the longest distance possible in 6 min with or without stopping. During the test, only standardized encouragement will be given to the patient. Pulsed oxygen saturation (SpO_2) and HR will be measured continuously during the test and recorded each minute with

a digital oximeter. The absolute and relative distance (6MWD), SpO_2, HR, rating of modified dyspnea Borg scale, walking duration if cessation occurs before 6 min and reasons for this cessation will be recorded. Distance will be compared with predicted values [27].

2.4.2.5. Bioimpedancemetry

Body composition will be assessed by a multi-frequency bioelectrical impedance analysis under standardized conditions (Bodystat impedancemeter, UK) [28–30]. The patient will be placed in a supine position for determining fat free mass, dry fat free mass and fat mass.

2.4.2.6. Maximum voluntary isometric quadriceps strength

The patient will sit on a recumbent chair (lower-limb training bench) with slight kyphosis and arms crossed over the chest [30,31]. The dominant lower limb will be tested with the knee placed at 90° flexion and a force gauge (Dynatrac strain gauge, Electronic Conseil, FR) attached to the ankle. The instruction provided by an experienced assessor will be standardized to obtain maximal contraction. The sustained time of contraction will be 5 sec each, and a resting period of 60 sec will be respected between each test. The first two attempts will be learning ones. A minimum of four and a maximum of 10 attempts will be made to ensure three values varying less than 10%. The maximum value obtained will be recorded. Strength will be compared with predicted values in kilograms [32].

2.4.2.7. Quality of life (QoL)

We will record QoL with two validated questionnaires for lung cancer patients. Cancer-related QoL will be assessed by the self-reported European Organization for Research

and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) including the lung cancer-specific questionnaire QLQ-LC13 [33].

2.4.2.8. Feasibility and safety

To evaluate the feasibility of this protocol, we will consider recruitment and adherence rates [15]. Recruitment rate will be defined as the ratio of patients who agree to participate in the study to those who are eligible. Adherence rate will be defined as the ratio of the number of completed training sessions to the number of expected sessions. Adherence will be considered acceptable with performance of 11 of the 15 expected exercise sessions. Adverse events will be systematically tracked during the study period and follow-up.

2.5. Recruitment procedures

Recruitment will be conducted in accordance with the Consort recommendations for non-pharmacological trials [34,35]. The study protocol was approved by the French regulatory authority for research (Agence Nationale de Sécurité du Médicament et des produits de santé, registration no.: 2016-A00622-49) and the Committee for Ethics (Comité de Protection des Personnes Sud-Est VI France, human research ethics approval no.: AU1267). All patients will receive an information form and be required to provide their written consent before entering this study protocol and performing any specific procedure. After the first surgical visit and the verification of eligibility, patients eligible for this protocol will be asked to participate. Patients agreeing to participate and having signed informed consent will be directed to the physiology lab for the first assessment visit (pre-intervention) before being assigned to one of the two study groups.

2.6. Randomization and allocation procedures

Randomization performed after the recruitment procedure, will involve a 1: 1 ratio, stratified by centre, centralized and in blocks of 5. The randomization sequence will be generated and managed electronically by a research manager independent of assessments or interventions. Allocation will be transmitted by emails send to all assessors and therapists involved. Allocation concealment is not possible in such an exercise training trial, and especially in a multicentre study, the physical evaluation and intervention could not be blinded.

2.7. Masking and blinding

In such a clinical experiment, blinding is not possible for patients and caregivers or assessors. However, the C group receiving only usual care will allow for demonstrating the beneficial effect of the intervention in the R group. To limit bias, we will ensure that assessors and caregivers will be different during the trial period. Moreover, we will ensure that participants do not meet each other.

2.8. Anticipated date of trial commencement and completion

The study started in April 2017 and will be completed in April 2019.

2.9. Statistical analysis including sample size calculation

Previous studies found a 4-day reduction in length of stay in patients completing an exercise training programme compared to usual care [36,37]. We chose a more conservative effect of the intervention. Our hypothesis is based on a one-sided decrease of 2 days' duration of hospital length of stay and considering a standard deviation of 3 days. With 90% power and a one-sided 5% type one error, 39 patients per group are required. Given a risk of dropout or

incomplete programme adherence (less than 11 sessions performed), we plan to increase the sample by 15% (i.e., 45 patients per group [total number = 90 patients]).

The analysis will be performed according to the intent-to-treat principle. Patients' characteristics per allocation group will be described by means, standard deviation, and range for quantitative outcomes or median and interquartile intervals with non-Gaussian distribution. For categorical parameters, counts and frequencies will be reported. The balance of main clinical parameters between allocation groups will be studied to verify randomization efficacy. The equilibrium of missing data will be checked to assess whether any attrition bias could lower the quality of conclusions. The primary outcome being hospital discharge ability, Student's t-test (unpaired) or Kruskal-Wallis H-test and Mood test (in case of abnormal distributions and/or heteroscedasticity) will be used to test the inter-group difference. Other quantitative outcomes (PFT, maximal respiratory pressures, CPET, 6MWD, maximum quadriceps voluntary strength, body composition and QoL) will be analysed by using the same tests. The inter-group difference for postoperative complication and mortality rates will be tested by chi-square test or Fisher exact test. Multivariate analysis of factors affecting hospital discharge ability or morbidity/mortality will involve ANOVA (mixed model) and logistic regression, respectively. The standard two-sided $p < 0.05$ will be used as a significance cutoff. Clinsight software will be used for randomization and data-management [Ennov Clinical v7.5, Ennov Group, Paris, FR] and SEM software for statistical calculation [38].

3. DISCUSSION

The beneficial effect of a short preoperative rehabilitation programme on length of stay after lung cancer resection in COPD patients remains to be robustly demonstrated. An improvement in physical fitness and decrease in complications were well shown after an exercise programme in this setting [9–11]. Improving the preoperative physical fitness in this specific population should limit the loss of postoperative respiratory function and exercise ability [12,14]. Other studies are needed to demonstrate that patients who undergo preoperative rehabilitation have better QoL and longer survival after lung surgery [14].

Mechanisms underlying decreased hospital discharge ability or postoperative complication rate need further investigation. Nevertheless, VO2peak is the strongest independent predictor of surgical complications and survival rates in NSCLC [6]. We hypothesize that increasing pre-surgical physical fitness and VO2peak should decrease hospital length of stay, postoperative complications and mortality in this population. Moreover, recent systematic reviews demonstrated these important outcomes [9–11]. Even more, a home-based programme should improve adherence to the programme without delaying the surgical treatment. Despite a short time course, the effectiveness of preoperative physical conditioning would increase and could explain the benefits on morbidity.

The safety and feasibility of such a standardized preoperative programme conducted at home should be confirmed because to the best of our knowledge, only an uncontrolled trial has been published to date [15].

Our study has some strengths. This is a multicentre RCT with a large sample (n=90 patients). All the lung resection procedures will be considered: lobectomy or pneumonectomy with video-assisted thoracic surgery or open thoracotomy. We acknowledge that the main limitation of our study is that patients and assessors will not be blinded to the intervention arm. However, we will ensure that assessors and therapists will be different during the trial

period. Concerning exercise training, blinding is not worth considering, but the comparison to the control group should demonstrate the efficacy of the rehabilitation programme. Finally, we cannot exclude that as part as the rehabilitation programme the visits of the physical therapist could provide psychological support to patients and would help with the improved condition before surgery.

4. CONCLUSION

The results of this original multicentre RCT of home-based rehabilitation should confirm the effectiveness of a short intensive home-based intervention for COPD patients eligible for lung cancer surgery. They could change practice before lung cancer resection thereby enabling preconditioning without delaying surgical treatment.

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CONTRIBUTORSHIP STATEMENT

HL, RR, FK, FC, MF designed the study and wrote the protocol.

GG, ET, EC, SA read and corrected the drafts.

COMPETING INTEREST

None to declare

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DATA SHARING STATEMENT

Not applicable

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FIGURE 1: Design and outcomes

TABLE 1: The 10-item list to assess the hospital discharge ability

The criteria considered for hospital discharge ability will be as follows:

- No chest tube for at least 24 hours
- Autonomy for feeding
- Autonomy for rising from bed
- Autonomy for toilet
- Autonomy for urinating and defecating
- Patient able to walk (2 lanes 30 m) without desaturation <90% on room air
- Patient able to go up and down one flight of stairs without desaturation <90% on room air (except handicap in which we consider the return to preoperative status)
- Satisfactory healing (parietal, thoracic and bronchopulmonary)
- No infusion
- No oxygen therapy

TABLE 2: Definitions for postoperative complications

- **Respiratory postoperative complications:**
  - Atelectasis: systematized ventilatory disorder objectified by chest radiography requiring enhanced management such as additional physical therapy sessions, bronchoscopy associated or not with non-invasive ventilation (NIV), maintenance or transfer to an intensive care unit (ICU)
  - Significant bronchial congestion characterized by difficult or spontaneous expectoration of bronchial secretions requiring enhanced management such as additional physical therapy sessions, bronchoscopy with or without NIV, maintenance or transfer to an ICU
  - Bronchospasm: occurrence or aggravation of dyspnea, wheezing at auscultation requiring a specific treatment
  - Respiratory failure requiring management in an ICU for NIV or intubation

- **Cardiovascular postoperative complications:**
  - Pulmonary embolism proven by angio-CTscan
  - Acute coronary syndrome
  - Circulatory failure defined by the need for specific inotropic treatment
  - Rhythm disorder requiring specific treatment

- **Infectious postoperative complications:**
  - Tracheobronchial infection, suspicion of pulmonary infection requiring antibiotic treatment, fever >38.5 °C, dirty sputum, hyperleucytosis >10000/mm^3, dubious radiological image, absence of pathogenic germs after culture of sputum and/or endobronchial samples
  - Postoperative pneumopathy: pulmonary infection requiring specific antibiotic treatment due to the presence of a pathogenic germs found after culture of sputum and/or endobrochial samples, associated with at least 2 other signs (a fever >38.5 °C, dirty sputum, hyperleucytosis >10000/mm^3, dubious radiological image)
  - Pneumopathy considered to be nosocomial (occurring after the 5th postoperative day)
  - Pleurisis requiring punction or redrainage for lobectomies

- **Other postoperative complications:**
  - Empyema
  - Bronchopleural fistula
  - Other (for example: urinary tract infection, bleeding)

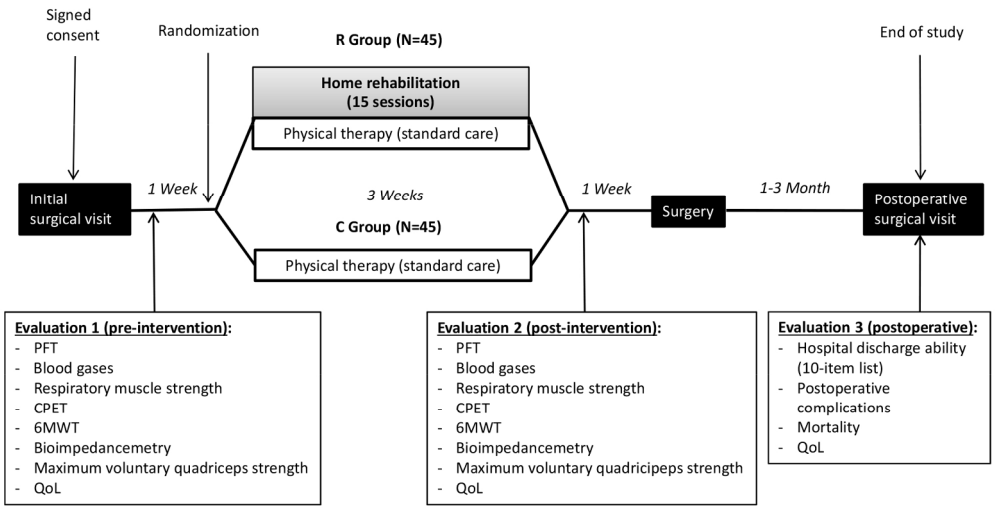

Figure 1: Design and outcomes

170x127mm (300 x 300 DPI)

Checklist of Items for Reporting Trials of Nonpharmacologic Treatments*

Section	Item	Standard CONSORT Description	Extension for Nonpharmacologic Trials	Reported on Page No.
Title and abstract†	1	How participants were allocated to interventions (e.g., "random allocation," "randomized," or "randomly assigned")	In the abstract, description of the experimental treatment, comparator, care providers, centers, and blinding status	1, 2
Introduction				
Background	2	Scientific background and explanation of rationale		4-6
Methods				
Participants†	3	Eligibility criteria for participants and the settings and locations where the data were collected	When applicable, eligibility criteria for centers and those performing the interventions	7, 8
Interventions†	4	Precise details of the interventions intended for each group and how and when they were actually administered	Precise details of both the experimental treatment and comparator	8-10
	4A		Description of the different components of the interventions and, when applicable, descriptions of the procedure for tailoring the interventions to individual participants	8-10
	4B		Details of how the interventions were standardized	8-10
	4C		Details of how adherence of care providers with the protocol was assessed or enhanced	Not applicable
Objectives	5	Specific objectives and hypotheses		6
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors)		10-14
Sample size†	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	When applicable, details of whether and how the clustering by care providers or centers was addressed	15, 16

Randomization–sequence generation†	8	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification)	When applicable, how care providers were allocated to each trial group	14, 15
Allocation concealment	9	Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned		14, 15
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups		14, 15
Blinding (masking)†	11A	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment	Whether or not those administering co-interventions were blinded to group assignment	15
	11B		If blinded, method of blinding and description of the similarity of interventions†	Not applicable
	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses	When applicable, details of whether and how the clustering by care providers or centers was addressed	16
Results				
Participant flow†	13	Flow of participants through each stage (a diagram is strongly recommended)---specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome; describe deviations from study as planned, together with reasons	The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center	Not applicable
Implementation of intervention†	New item		Details of the experimental treatment and comparator as they were implemented	Not applicable
Recruitment	14	Dates defining the periods of recruitment and follow-up		Not applicable
Baseline data†	15	Baseline demographic and clinical characteristics of each group	When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group	Not applicable

Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether analysis was by "intention-to-treat"; state the results in absolute numbers when feasible (e.g., 10/20, not 50%)		Not applicable
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (e.g., 95% confidence interval)		Not applicable
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory		Not applicable
Adverse events	19	All important adverse events or side effects in each intervention group		Not applicable
Discussion				
Interpretation†	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes	In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group	17, 18
Generalizability†	21	Generalizability (external validity) of the trial findings	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial	17, 18
Overall evidence	22	General interpretation of the results in the context of current evidence		17, 18

*Additions or modifications to the CONSORT checklist. CONSORT = Consolidated Standards of Reporting Trials.
†This item was modified in the 2007 revised version of the CONSORT checklist.

BMJ Open

Effect of an intensive 3-week preoperative home rehabilitation programme in chronic obstructive pulmonary disease patients eligible for lung cancer surgery: A multicentre randomized controlled trial

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Title: Effect of an intensive 3-week preoperative home rehabilitation programme in chronic obstructive pulmonary disease patients eligible for lung cancer surgery: A multicentre randomized controlled trial

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Effect of an intensive 3-week preoperative home rehabilitation programme in chronic obstructive pulmonary disease patients eligible for lung cancer surgery: A multicentre randomized controlled trial

ABSTRACT (296 words/300 max)

Introduction: Surgery is the standard curative treatment for lung cancer but is only possible in patients with local tumour and preserved exercise capacity. Improving fitness before surgery can reduce postoperative complications and mortality. However, preoperative rehabilitation remains difficult to implement for several reasons. We aim to investigate the effectiveness of an intensive 3-week home-based preoperative exercise training programme on hospital discharge ability, postoperative complications and physical performance in patients with chronic obstructive pulmonary disease (COPD) who are eligible for lung cancer surgery.

Methods and analysis: We designed a multicentre randomized controlled trial. The randomization sequence will be generated and managed electronically by a research manager independent of assessments or interventions. We will recruit 90 patients with COPD and a diagnosis of lung cancer from four university hospitals. The rehabilitation group (R group) will receive a standardized preoperative home exercise programme for 3 weeks, combining both high-intensity training and usual physical therapy. The R group will perform 15 training sessions over 3 weeks on a cycloergometer. A physical therapist experienced in pulmonary rehabilitation will visit the patient at home and supervise one session a week. The R group will be compared to a control group receiving preoperative usual physical therapy only. The primary outcome will be hospital discharge ability assessed with a 10-item list. Secondary outcomes will be postoperative course (complication rate and mortality) as well as pulmonary

function, exercise capacity and quality of life assessed 1 month before and the day before surgery.

Ethics and dissemination: This protocol has been approved by the French health authority for research (2016-A00622-49) and the research ethics committee/institutional review board (AU1267). Adverse events that occur during the protocol will be reported to the principal investigator. The results will be published in an international peer-reviewed journal.

Trial registration number: NCT 03020251

KEYWORDS (5/5 max): exercise, lung resection, physical therapy, postoperative complications, rehabilitation

STRENGTHS AND LIMITATIONS OF THIS STUDY (4/5 max)

- This is a multicentre randomized controlled trial
- The trial will include a large number of participants (n=90 patients)
- The trial will include COPD patients presenting lung cancer (or high suspicion for malignant tumour) eligible for resection surgery (lobectomy or pneumonectomy with video-assisted thoracic surgery or open thoracotomy)
- There is no assessor or patient blinding

1. INTRODUCTION

Lung cancer is the fourth most frequent cancer in the world but the first cause of cancer-related death worldwide [1,2]. Among treatments, surgery is conducted with a curative intent generally in patients with early TNM disease stages (stages I, II and IIIA) and preserved exercise capacity [3]. However, only 25% of patients are considered suitable for surgery because of advanced-stage disease or poor functional status [4].

Despite the operative risk assessment, the incidence of postoperative respiratory complications and overall complications are respectively 15% and 30% after lung resection for cancer [5]. Patients with a complicated postoperative course have a longer hospital length of stay, more frequent stay in an intensive care unit (ICU) and higher mortality rate [5].

Furthermore, peak oxygen uptake (VO2peak) is reported to be the strongest independent predictor of surgical complications and survival rates with non-small cell lung cancer (NSCLC) [6]. Performance during field tests are equally major determinants of morbidity and mortality after lung resection [6]. Surgery itself leads to a 13% to 28% decrease in VO2peak [7], lasting up to 24 months after resection [8]. The existence of chronic obstructive pulmonary disease (COPD) or cardiovascular comorbidities may further decrease VO2peak [7]. Chemotherapy and/or radiotherapy are associated with additional impairment of exercise capacity [8].

The beneficial effects of preoperative rehabilitation are objectified by physiological parameters and surgical outcomes, but the level of evidence is deemed insufficient [9–11]. A recent Cochrane review emphasized the disparities between studies and the need for larger high-quality randomized controlled trials (RCTs) in this area [11]. Future research must focus on patient-tailored exercise programmes and determine the influence of coexisting comorbidities on outcomes. Moreover, preoperative exercise therapy and exercise modalities including timing and training volume should be detailed and compared. Preoperative home

rehabilitation should be particularly investigated to make readaptation programmes more accessible and to reduce costs for in- and/or outpatient programmes. The feasibility, safety and effectiveness of preoperative interventions performed in a home setting for a short period have been demonstrated [12,13].

Additionaly, rehabilitation programmes are not yet substantially developed, primarily because of fear of tumour progression by delaying surgery and the difficulty in organizing such programmes or the lack of experienced physical therapists.

In light of the current literature, we implemented a multicentre RCT of an intensive 3-week preoperative home rehabilitation programme for COPD patients eligible for lung resection. We aim to investigate the effectiveness of a home-based preoperative exercise training programme on hospital discharge ability, postoperative complications and physical performance.

2. METHODS

2.1. Setting

This prospective, multicentre, open-label RCT will be conducted in 4 French university hospitals.

2.2 Participants

2.2.1. Inclusion criteria

We will include patients with the following conditions:

- Lung cancer (or high suspicion for malignant tumour) eligible for resection surgery (lobectomy or pneumonectomy with video-assisted thoracic surgery or open thoracotomy)
- COPD stages from 2 to 4 by the Gold classification (FEV1/FVC<70%, FEV1<80% of predicted value)
- Exertional dyspnoea stage mMRC≥1
- Receiving written information and giving signed consent
- Affiliated with the French social health insurance.

2.2.2. Non-inclusion criteria

We will exclude patients with the following conditions:

- COPD stage 1 by the Gold classification (FEV1≥80% of predicted value)
- Contraindication to surgery based on the initial cardiopulmonary exercise test (CPET) [6]
- Cardiac or vascular contraindication to the rehabilitation programme
- Living alone at home (to ensure safety during the training sessions)

- Under ventilator assistance at home [oxygen therapy or non-invasive ventilation (NIV)]
- Exercise hypoventilation ($PaCO_2$>45 mmHg)
- Cognitive impairment
- Legally incapacitated
- Pregnancy.

2.3. Details of the intervention and control

2.3.1. Rehabilitation group

The rehabilitation group (R group) will undergo both a standardized preoperative high-intensity training programme performed at home and standardized physical therapy sessions according to usual care. Over 3 weeks, the patients will perform 15 sessions of rehabilitation (5 days/week) including 1 supervised session performed per week. The cycloergometer will be installed by the service provider who will organize home care in each centre. These training sessions will be supervised by physical therapists familiar with these programmes. The study will not lead to delay in the treatment and the surgical management.

The rehabilitation programme will involve endurance cycloergometer training with heart rate (HR) monitoring.

The first week of training (W1) will consist of a continuous endurance training regime. W1 will allow for assessing the patient's ability to complete the training course and to teach them how to perform it well. The session will include a 5-min warm-up cycloergometer workload fixed to the ventilatory threshold determined during the CPET or at 60% of maximum workload, if the ventilatory threshold was not detectable. The exercise session will last at least 30 min, which can be separated by rest periods.

Weeks 2 and 3 of training (W2 and W3) will consist of a high-intensity interval training regime. The reduced volume of training and shorter session duration required with high-intensity interval training to obtain physical benefits versus continuous training should be more acceptable for patients still engaged in several preoperative exams and preoperative care [14]. The longer rest period between each high-intensity interval training session will optimize recuperation time and favour adherence [14]. The course of high-intensity sessions will be at least 10 repetitions of 30 sec at maximum workload and 60 sec at the ventilatory threshold level.

The intensity of the exercise and number of repetitions will be adjusted weekly to maintain the targeted HR within 5 beats/min.

A physical therapist experienced in pulmonary rehabilitation will visit the patient at home and supervise one session per week (at the beginning of each of the three weeks: the 1st, 6th and 11th exercise session). The therapist will check the initial intensity and progression of the training sessions. Non-supervised sessions will be performed during the week and not during the weekend to allow for email or phone contact with the physical therapist. The patient will complete a diary to collect the duration and intensity of the cycling exercise, mean HR and number of repetitons. We will record the number of exercise session(s) performed and the reason(s) for not performing exercise.

The rehabilitation programme will also include muscle strengthening exercises for upper arms and standardized usual physical therapy.

Upper-arm exercises will be performed on the same days after the cycling exercise. A rest period will be respected according to patients' needs between the endurance and the strength training workouts. Shoulder (deltoid, pectoral and dorsal muscles), elbow (biceps and triceps muscles), wrist (flexors and extensors muscles) muscles will be trained with elastics or dumbbells. For each muscle groups, 3-5 sets of 8-10 repetitions will be performed starting

with the lowest resistance. Depending on the patient perception, the resistance will be increased.

2.3.2. Control group

A control group (C group) will perform 15 standardized preoperative physical therapy sessions according to usual care. The sessions will consist of 30 min of standardized preoperative physical therapy performed 5 days/week for 3 weeks. They will be standardized with a written prescription and will include airway clearance techniques, deep breathing exercises emphasizing inspiration and thoracic stretching. According to current recommendations, the C group will be advised to be physically active.

2.4. Primary and secondary outcome measures and assessment point

Measurements are presented in *figure 1*. The primary outcome will be hospital discharge ability assessed by a 10-item list. The secondary outcomes will be postoperative course (complication rate and mortality), pulmonary function, exercise capacity, and quality of life. Surgical complications and survival rate with NSCLC are predicted by VO2peak, a surrogate of patient fitness [6]. Thus, postoperative morbidity should be improved by the exercise training programme [9,10].

Participants will undergo all assessments in the physiology laboratory on the same day so as to limit transport and fatigue. Baseline assessments will be performed 1 month before surgery (pre-intervention or first evaluation) and will be repeated the day before surgery (post-intervention or second evaluation). To ensure reproductibility of the assessments, the order will be standardized: pulmonary function tests, maximal respiratory pressure measurements, cardiopulmonary exercise test, bioimpedancemetry, maximum voluntary

isometric quadriceps strength measurement, 6-min walk test (6MWT) and quality of life. The rest period will be respected according to patients' needs.

2.4.1. Primary outcome

We will consider hospital discharge ability assessed by a 10-item list that reflects clinical assessments. Our 10-item list assessing hospital discharge ability was developed by a panel of therapists including thoracic surgeons, physiologists, a physical medicine physician and physical therapists. We considered this outcome to be more relevant than true hospital length of stay, which is affected by circumstances non-related with patient condition (e.g., possibility or not for discharge during the weekend, therapeutic care facilities at home, transfer to a rehabilitation centre). The period considered for discharge ability will be the interval between the day of surgery (D0) and the day (Dn) when the 10 items are satisfied (*Table 1*). It will be recorded daily by therapists of the surgical staff in charge of the patient.

2.4.2. Secondary outcomes

2.4.2.1. Postoperative course

The postoperative course will be assessed daily by therapists of the surgical staff in charge of the patient and by information from the patient's file. We will record the number of postoperative complications (pulmonary, cardiovascular, infectious, and general – see *Table 2* for respective definitions [15,16]) observed during the stay in surgery or ICU departments, mortality rate, hospital length of stay, chest tube duration, number of NIV sessions, ICU length of stay and reasons.

2.4.2.2. Pulmonary function test (PFT)

The test will determine static pulmonary volumes and flow rates (flow/volume curve) according to international recommendations by use of a body plethysmograph (Bodybox Jaeger Care fusion, USA) [17]. A measure of the alveolar-capillary diffusion capacity for carbon monoxide (DLCO) will involve the apnea method. All measurements will be expressed as a percentage of reference values [18]. Arterial blood gases (PaO_2, $PaCO_2$, and pH) at rest will be measured by arterial sampling or arterialized capillary sampling at the ear lobe [19]. Maximum respiratory pressures (inspiratory and expiratory pressures at mouth, and nasal inspiratory pressure) will be measured in accordance with the American Thoracic Society and European Respiratory Society recommendations [20] and compared with predicted values [21].

2.4.2.3. Cardiopulmonary exercise test (CPET)

The patient will perform a standardized incremental test following the American Thoracic Society and American College of Chest Physician guidelines [22]. The test will be performed on a cycloergometer until exhaustion, with continuous recording by 12-lead electrocardiography and breath-by-breath expired gas analysis (CPX MedGraphics, St Louis, USA) [22]. The workload increments will be defined according to predicted maximal power output (Wmax), with a first stage of warm-up corresponding to 30% Wmax and 10 following stages to complete the test in 12 to 15 min. The ventilatory threshold will be determined by the Beaver method. Wmax and VO2peak will be measured at the end of the last exercise level maintained for at least 30 sec. Symptoms will be rated on a 10-point Borg scale. Blood gases will be measured at the end of the test. Reference values for exercise testing values will be from Jones [23].

2.4.2.4. 6-min walk test (6MWT)

The 6MWT will be conducted according to the American Thoracic Society and European Respiratory Society recommendations in 30-m corridor [24]. Patients will be instructed to cover the longest distance possible in 6 min with or without stopping. During the test, only standardized encouragement will be given to the patient. Pulsed oxygen saturation (SpO_2) and HR will be measured continuously during the test and recorded each minute with a digital oximeter. The absolute and relative distance (6MWD), SpO_2, HR, rating of modified dyspnoea Borg scale, walking duration if cessation occurs before 6 min and reasons for this cessation will be recorded. Distance will be compared with predicted values [25]. A rest duration of at least 45 min will be respected between CPET and 6MWT.

2.4.2.5. Bioimpedancemetry

Body composition will be assessed by a multi-frequency bioelectrical impedance analysis under standardized conditions (Bodystat impedancemeter, UK) [26–28]. The patient will be placed in a supine position for determining fat free mass, dry fat free mass and fat mass.

2.4.2.6. Maximum voluntary isometric quadriceps strength

The patient will sit on a recumbent chair (lower-limb training bench) with slight kyphosis and arms crossed over the chest [28,29]. The dominant lower limb will be tested with the knee placed at 90° flexion and a force gauge (Dynatrac strain gauge, Electronic Conseil, FR) attached to the ankle. The instruction provided by an experienced assessor will be standardized to obtain maximal contraction. The sustained time of contraction will be 5 sec each, and a resting period of 60 sec will be respected between each test. The first two attempts will be learning ones. A minimum of four and a maximum of 10 attempts will be made to

ensure three values varying less than 10%. The maximum value obtained will be recorded. Strength will be compared with predicted values in kilograms [30].

2.4.2.7. Quality of life (QoL)

We will record QoL with two validated questionnaires for lung cancer patients. Cancer-related QoL will be assessed by the self-reported European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) including the lung cancer-specific questionnaire QLQ-LC13 [31].

2.4.2.8. Feasibility and safety

To evaluate the feasibility of this protocol, we will consider recruitment and adherence rates [13]. Recruitment rate will be defined as the ratio of patients who agree to participate in the study to those who are eligible. Adherence rate will be defined as the ratio of the number of completed training sessions to the number of expected sessions. Adherence will be considered acceptable with performance of 11 of the 15 expected exercise sessions. Adverse events will be systematically tracked during the study period and follow-up.

2.5. Ethics

Recruitment will be conducted in accordance with the Consort recommendations for non-pharmacological trials [32,33]. The study protocol was approved by the French regulatory authority for research (Agence Nationale de Sécurité du Médicament et des produits de santé, registration no.: 2016-A00622-49) and the research ethics committee/institutional review board (REC/IRB: Comité de Protection des Personnes Sud-Est VI France, human research ethics approval no.: AU1267). The same applies for the implementation of changes introduced by amendments. All patients will receive an

information form and be required to provide their written consent before entering this study protocol and performing any specific procedure. After the first surgical visit and the verification of eligibility, patients eligible for this protocol will be asked to participate. Patients agreeing to participate and having signed informed consent will be directed to the physiology lab for the first assessment visit (pre-intervention) before being assigned to one of the two study groups.

Pursuant to the provisions concerning the confidentiality of data that are available to persons responsible for quality control of biomedical research and pursuant to the provisions on confidentiality of information, persons with direct access will take all necessary precautions to ensure the confidentiality of information in particular as regards to the identity of patient and to results achieved. For biomedical research or its outcome, the data collected on people who are suitable and transmitted to the sponsor by the investigator will be made anonymous.

2.6. Randomization and allocation procedures

Randomization performed after the recruitment procedure, will involve a 1: 1 ratio, stratified by centre, centralized and in blocks of 5. The randomization sequence will be generated and managed electronically by a research manager independent of assessments or interventions. Allocation will be transmitted by emails send to all assessors and therapists involved. Allocation concealment is not possible in such an exercise training trial, and especially in a multicentre study, the physical evaluation and intervention could not be blinded.

2.7. Masking and blinding

In such a clinical experiment, blinding is not possible for patients and therapists or assessors. However, the C group receiving only usual care will allow for demonstrating the

beneficial effect of the intervention in the R group. To limit bias, we will ensure that assessors and therapists will be different during the trial period. Moreover, we will ensure that participants do not meet each other.

2.8. Anticipated date of trial commencement and completion

The study started in April 2017 and will be completed in July 2019. The enrollment period is of 24 months and patient's participation duration is of 3 months.

2.9. Statistical analysis including sample size calculation

Previous studies found a 4-day reduction in length of stay in patients completing an exercise training programme compared to usual care [34,35]. We chose a more conservative effect of the intervention. Our hypothesis is based on a one-sided decrease of 2 days' duration of hospital length of stay and considering a standard deviation of 3 days. With 90% power and a one-sided 5% type one error, 39 patients per group are required. Given a risk of dropout or incomplete programme adherence (less than 11 sessions performed), we plan to increase the sample by 15% (i.e., 45 patients per group [total number = 90 patients]).

The analysis will be performed according to the intent-to-treat principle. Patients' characteristics per allocation group will be described by means, standard deviation, and range for quantitative outcomes or median and interquartile intervals with non-Gaussian distribution. For categorical parameters, counts and frequencies will be reported. The balance of main clinical parameters between allocation groups will be studied to verify randomization efficacy. The equilibrium of missing data will be checked to assess whether any attrition bias could lower the quality of conclusions. The primary outcome being hospital discharge ability, Student's t-test (unpaired) or Kruskal-Wallis H-test and Mood test (in case of abnormal distributions and/or heteroscedasticity) will be used to test the inter-group difference. Other

quantitative outcomes (PFT, maximal respiratory pressures, CPET, body composition, maximum quadriceps voluntary strength, 6MWD and QoL) will be analysed by using the same tests. The inter-group difference for postoperative complication and mortality rates will be tested by chi-square test or Fisher exact test. Multivariate analysis of factors affecting hospital discharge ability or morbidity/mortality will involve ANOVA (mixed model) and logistic regression, respectively. The standard two-sided $p<0.05$ will be used as a significance cutoff. Clinsight software will be used for randomization and data-management [Ennov Clinical v7.5, Ennov Group, Paris, FR] and SEM software for statistical calculation [36].

2.10. Data collection, quality management and dissemination

Data from the study will be collected by the clinical research associate in charge of the study, under the responsibility of the physician coordinator of the study. For each patient enrolled, an electronic case report form (CRF) must be completed and signed by the principal investigator or authorized delegate from the study staff. Data entry will be in Ennov Clinical. A Clinical Research Associate (CRA) mandated by the promoter will ensure the successful completion of the study, the collection of data generated in writing, documentation, record and report in accordance with the standard operating procedures and the good clinical practice and current French laws. The data set will be the property of the sponsor. However, the principal investigator, the project manager and the statistician (Data monitoring committe) will have full access to the final data set. The results will be presented at an international congress and published in a peer-reviewed journal.

3. DISCUSSION

An improvement in physical fitness and decrease in complications were well shown after an exercise programme in this setting [9–11]. Improving the preoperative physical fitness in this specific population should limit the loss of postoperative respiratory function and exercise ability [12,37]. This is the real challenge of all staff taking care of these patients. The beneficial effect of a short preoperative rehabilitation programme on length of stay after lung cancer resection in COPD patients remains to be robustly demonstrated as emphasized by the recent Cochrane review [11]. Other studies are needed to demonstrate that patients who undergo preoperative rehabilitation have better QoL and longer survival after lung surgery [12].

Mechanisms underlying decreased hospital discharge ability or postoperative complication rate need further investigation [11]. Nevertheless, VO2peak is the strongest independent predictor of surgical complications and survival rates in NSCLC [6]. We hypothesize that increasing pre-surgical physical fitness and VO2peak should decrease hospital length of stay, postoperative complications and mortality in this population. Moreover, recent systematic reviews demonstrated these important outcomes [9–11]. Even more, a home-based programme should improve adherence to the programme without delaying the surgical treatment and limit costs. In the future it could permit to make eligible to surgery a more important number of COPD patients with NSCLC. Despite a short time course, the effectiveness of preoperative physical conditioning would increase and could explain the benefits on morbidity.

The safety and feasibility of such a standardized preoperative programme conducted at home should be strengthen because to the best of our knowledge, only an uncontrolled trial has been published to date [13].

Our study has some strengths. This is the first multicentre RCT with a large sample (n=90 patients) implementing short course preoperative high intensity training at home in COPD patients with NSCLC. All the lung resection procedures are considered: lobectomy or pneumonectomy with video-assisted thoracic surgery or open thoracotomy. We acknowledge that the main limitation of our study is that patients and assessors will not be blinded to the intervention arm. However, we will ensure that assessors and therapists will be different during the trial period. Concerning exercise training, blinding is not worth considering, but the comparison to the control group should demonstrate the effectiveness of the rehabilitation programme. Finally, we cannot exclude that as part as the rehabilitation programme the visits of the physical therapist could provide psychological support to patients and would help with the improved condition before surgery.

The results of this original multicentre RCT of home-based rehabilitation could strengthen the effectiveness of a short intensive home-based intervention for COPD patients eligible for lung cancer surgery. They could change practice before lung cancer resection thereby enabling preconditioning without delaying surgical treatment.

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CONTRIBUTORSHIP STATEMENT

HL, RR, FK, FC, MF designed the study and wrote the protocol.

GG, ET, EC, SA read and corrected the drafts.

HL, FK, FC, MF, GG, ET collected and managed the data

HL, FK, FC, MF, GG, ET will analyse and interpret the data

COMPETING INTEREST

None to declare

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DATA SHARING STATEMENT

Not applicable

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FIGURE 1: Design and outcomes

TABLE 1: The 10-item list to assess the hospital discharge ability

The criteria considered for hospital discharge ability will be as follows:

- No chest tube for at least 24 hours
- Autonomy for feeding
- Autonomy for rising from bed
- Autonomy for toilet
- Autonomy for urinating and defecating
- Patient able to walk (2 lanes 30 m) without desaturation <90% on room air
- Patient able to go up and down one flight of stairs without desaturation <90% on room air (except handicap in which we consider the return to preoperative status)
- Satisfactory healing (parietal, thoracic and bronchopulmonary)
- No infusion
- No oxygen therapy

TABLE 2: Definitions for postoperative complications

- **Respiratory postoperative complications:**
  - Atelectasis: systematized ventilatory disorder objectified by chest radiography requiring enhanced management such as additional physical therapy sessions, bronchoscopy associated or not with non-invasive ventilation (NIV), maintenance or transfer to an intensive care unit (ICU)
  - Significant bronchial congestion characterized by difficult or spontaneous expectoration of bronchial secretions requiring enhanced management such as additional physical therapy sessions, bronchoscopy with or without NIV, maintenance or transfer to an ICU
  - Bronchospasm: occurrence or aggravation of dyspnea, wheezing at auscultation requiring a specific treatment
  - Respiratory failure requiring management in an ICU for NIV or intubation

- **Cardiovascular postoperative complications:**
  - Pulmonary embolism proven by angio-CTscan
  - Acute coronary syndrome
  - Circulatory failure defined by the need for specific inotropic treatment
  - Rhythm disorder requiring specific treatment

- **Infectious postoperative complications:**
  - Tracheobronchial infection, suspicion of pulmonary infection requiring antibiotic treatment, fever >38.5 °C, dirty sputum, hyperleucytosis >10000/mm^3, dubious radiological image, absence of pathogenic germs after culture of sputum and/or endobronchial samples
  - Postoperative pneumopathy: pulmonary infection requiring specific antibiotic treatment due to the presence of a pathogenic germs found after culture of sputum and/or endobrochial samples, associated with at least 2 other signs (a fever >38.5 °C, dirty sputum, hyperleucytosis >10000/mm^3, dubious radiological image)
  - Pneumopathy considered to be nosocomial (occurring after the 5th postoperative day)
  - Pleurisis requiring punction or redrainage for lobectomies

- **Other postoperative complications:**
  - Empyema
  - Bronchopleural fistula
  - Other (for example: urinary tract infection, bleeding)

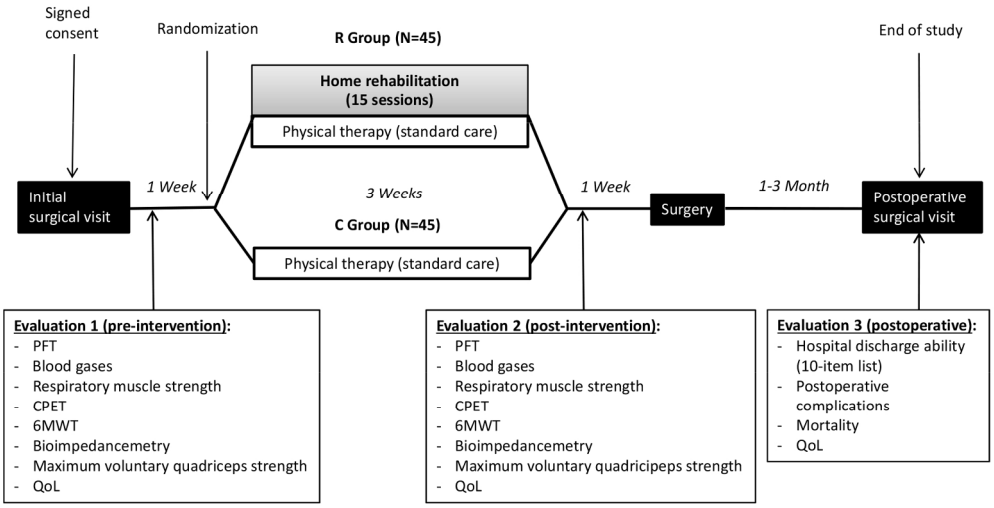

FIGURE 1: Design and outcomes

170x127mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, 3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 15
	2b	All items from the World Health Organization Trial Registration Data Set	1-31
Protocol version	3	Date and version identifier	See full protocol document
Funding	4	Sources and types of financial, material, and other support	4, 15, 23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 2, 21
	5b	Name and contact information for the trial sponsor	1, 2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18, 21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15, 16, 18, 21
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6, 7
	6b	Explanation for choice of comparators	6, 7
Objectives	7	Specific objectives or hypotheses	7

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7, 16
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8, 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8, 9, 15, 16
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10, 15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11, 12, 29
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17, 18
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10, 15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15, 16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16-17
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-15,17, 18, 21
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15-18
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18, 21
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17, 18, 21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17, 18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17, 18

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18, 21
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18, 21
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15, 16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	15, 16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15, 16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15, 16
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15, 16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	16, 18, 21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	17, 18

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See full protocol document
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.